

Hormone Therapy and Coronary Heart Disease

Evolving evidence from clinical trials

KEY POINTS

- Substantial evidence indicates that in premenopausal women, endogenous estrogen may slow the development of coronary heart disease. Younger menopausal age is significantly associated with higher risk of coronary heart disease.
- Exogenous estrogen administered shortly after menopause may retard the development of atherosclerosis by beneficial effects on blood lipids and endothelial function.
- Recent reanalysis of data from the Women's Health Initiative revealed that the hazard ratio for coronary heart disease with all hormone therapy was 0.76 for women who were less than 10 years from menopause at the start of the study.
- The Nurses' Health Study showed that when hormone therapy was initiated within 4 years of menopause, the risk of coronary heart disease was significantly reduced for estrogen alone or combination therapy.

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Evidence regarding the relation of estrogen and coronary heart disease (CHD) is evolving as new information becomes available. CHD is very uncommon in women of reproductive age. Before age 50 years, the incidence of myocardial infarction (MI) is much more common in men than in women.¹ The incidence of MI increases in individuals of both genders as they age, but after menopause the rate of increase is greater in women than men, and the incidence becomes similar in both genders after age 80 years. Data from the Nurses' Health Study found a significant association between younger menopausal age and higher risk for CHD.²

Estrogen and the development of CHD

A substantial body of evidence indicates that endogenous estrogen may

retard the development of CHD in premenopausal women. Joakimsen et al found that there was a significant inverse relation between age of menopause and extent of carotid artery atherosclerosis observed sonographically.³ Premenopausal women with bilateral oophorectomy have a markedly increased risk of coronary atherosclerosis, and the risk of MI is inversely related to the age at which oophorectomy occurs.⁴ The Framingham study showed that the incidence of cardiovascular events was lower in premenopausal than postmenopausal women of the same age.⁵

A large number of studies also indicate that exogenous estrogen has a similar effect in postmenopausal women. Exogenous estrogen may prevent the development of CHD in postmenopausal women by several mechanisms. After menopause in women not receiving exogenous estrogen, high-density lipoprotein cholesterol (HDL-C) levels decrease and low-density lipoprotein-cholesterol (LDL-C) levels increase. A major effect of exogenous estrogen is to increase circulating levels of the cardioprotective HDL-C and lower circulating levels of the deleterious LDL-C.⁶ Other mechanisms whereby estrogen prevents coronary artery atherosclerosis include increasing coronary artery blood flow, promoting coronary artery

vasodilatation, preventing platelet aggregation, improving cardiac contractility, decreasing lipoprotein(a), and inhibiting LDL-C oxidation. The elegant studies by Clarkson et al in the nonhuman primate found that when estrogen is given immediately after bilateral oophorectomy, it markedly reduces the development of coronary artery atherosclerosis compared with animals receiving a placebo.⁷

Progression of subclinical atherosclerosis

Intima-media thickness of the arterial wall is the earliest detectable anatomic change in the development and progression of atherosclerosis. It has been shown that carotid artery intima-media thickness is a marker of generalized atherosclerosis and is a predictor of clinical cardiovascular events. Hodis et al performed a prospective randomized clinical trial on a group of 222 postmenopausal women with a mean age of 62 years without pre-existing cardiovascular disease (Estrogen Replacement and Atherosclerosis Trial).⁸ The women were randomized to receive either 1 mg estradiol orally once a day or placebo for 2 years. Carotid artery ultrasound was used to measure the intima-media thickness in the right distal common carotid artery every 6 months for 2 years. After 2 years, the women in this study receiving estrogen had no increase in the mean carotid artery intima-media thickness (-0.0017 mm/year), while the group receiving placebo had a significant increase in the mean intima-media thickness of this artery (0.0036 mm/year). This study provided a high level of evidence that administration of exogenous estrogen to women without evidence

of carotid artery atherosclerosis retards the progression of subclinical atherosclerosis.

Consistent with these findings, many observational epidemiologic studies reported that administration of estrogen to postmenopausal women reduces the incidence of coronary artery disease (CAD) and prevents MI. More than 40 observational epidemiologic studies have shown that administration of estrogen to postmenopausal women substantially reduces both cardiovascular morbidity and mortality. In these observational studies, estrogen use by postmenopausal women was associated with a reduced risk of developing CHD, with the odds ratio in the studies ranging from 0.39 to 0.81 compared with non-estrogen users.⁹ An 8.5-year multicenter cohort study from the Lipid Research Clinics program of 2270 white women reported the multivariate adjusted relative risk (RR) of cardiovascular mortality with estrogen use was 0.37 (confidence interval [CI], 0.16-0.58).¹⁰

The largest observational cohort study that investigated the relation of estrogen to CHD in postmenopausal women is the Nurses' Health Study. This study was begun in 1976, when 121,700 female nurses aged 30 to 55 years completed a mailed questionnaire about their use of hormones postmenopausally and their medical history, including cardiovascular disease. Follow-up questionnaires were mailed every 2 years and follow-up data were available for more than 90% of the cohort. In the 20 years of follow-up from 1976 to 1996, a total of 70,533 nurses were or became postmenopausal, and 808,825 person-years of follow-up were accumulated.¹¹ The multivariate adjusted RR of major CHD, which includes non-fatal MI, fatal CAD, coronary bypass surgery, or angioplasty was 0.61 (CI, 0.52-0.71) for current users

of hormone therapy. The RR was 0.55 (CI, 0.45-0.68) for users of oral conjugated estrogen alone and 0.64 (CI, 0.49-0.85) for users of estrogen with progestin, compared with the risk of women not taking hormones.

The Women's Health Initiative

Despite the large number of women in these observational studies, there was concern that selection bias could have influenced the results, because women taking hormones were presumed to have healthier lifestyles and be of higher socioeconomic class than non-users. To address this problem, the National Institutes of Health initiated a series of large randomized clinical trials of postmenopausal women. The primary purpose of these trials was to focus on the risks and benefits of certain strategies that could possibly reduce the risk of cardiovascular disease, cancer, and fracture in postmenopausal women. Each of these trials was designed by a group of investigators, and the entire series of studies was designated as the Women's Health Initiative (WHI).

The WHI enrolled 161,809 postmenopausal women between 1993 and 1998 for this series of trials. The WHI enrolled predominantly healthy women, in contrast to other studies that analyzed the effect of estrogen in postmenopausal women with pre-existing CHD. In the Heart and Estrogen Replacement Study (HERS)¹² and Estrogen Replacement and Atherosclerosis Trial,¹³ estrogen did not prevent progression of atherosclerosis in women with established CHD. One of the WHI randomized trials enrolled 16,608 postmenopausal women aged 50 to 79 years with an intact uterus who were randomized to receive either 0.625 mg conjugated equine estrogen (CEE) with 2.5 mg medroxyprogesterone acetate (MPA)

in a single pill, or placebo.¹⁴ The primary outcome of this trial was CHD. The mean age of the women in this trial at the time of initial screening was 63 years, with one third of the women aged 50 to 59 years, about 45% aged 60 to 69 years, and 21% aged 70 to 79 years. The planned duration of the study was 8.5 years. However, the study was stopped prematurely after a mean 5.2 years of follow-up because the risk of developing breast cancer in the hormone group exceeded the stopping boundary.

In contrast to the findings of the numerous observational studies, the results of this WHI study showed that women taking the hormones had an increased risk of CHD (acute MI), silent MI, or CHD death, with a hazard ratio (HR) of 1.29 (CI, 1.02-1.63). Subsequent analysis of this WHI study reported an adjusted HR rate of CHD of 1.24 with hormone therapy (CI, 1.00-1.54).¹⁵ The increased risk of CHD was significant only in the first year of treatment (HR, 1.81; CI, 1.09-3.01). There was a lower nonsignificant increase in CHD for hormone users during years 2 to 5 of the study and a nonsignificant decrease (HR, 0.70; CI, 0.42-1.14) in women with 6 or more years' duration in the study. When the data were analyzed by subgrouping the women into 3 groups by years since menopause, the only significant increased risk of CHD with hormone use occurred in women who were 20 or more years postmenopausal at the time of enrollment (HR, 1.71). Women 10 to 14 years postmenopausal had an insignificant increase in CHD with hormone use (HR, 1.22), while women less than 10 years postmenopausal had an insignificant decrease in CHD (HR, 0.89). Therefore, this analysis of the data

TABLE 1

Hazard Ratios*: CHD Events by Years Since Menopause

	Years Since Menopause at Baseline		
	<10 y	10-19 y	≥20 y
All HT	0.76 (0.50-1.16)	1.10 (0.84-1.45)	1.28 (1.03-1.58)
CEE	0.48 (0.20-1.17)	0.96 (0.64-1.44)	1.12 (0.86-1.46)
CEE + MPA	0.88 (0.54-1.43)	1.23 (0.85-1.77)	1.66 (1.14-2.41)

CEE, conjugated equine estrogen; CHD, coronary heart disease; HT, hormone therapy; MPA, medroxyprogesterone acetate.

*Hazard ratio (95% confidence interval).

Modified from Rossouw JE, et al. *JAMA*. 2007;297:1465-1477.

TABLE 2

Current Hormone Use and Risk of Major CHD

	RR (95% CI) Multivariate-Adjusted	
	Within 4 y	≥10 y
Never	1.0 (reference)	1.0 (reference)
ET	0.66 (0.54-0.80)	0.76 (0.57-1.00)
EPT	0.72 (0.56-0.92)	0.80 (0.53-1.23)

CHD, coronary heart disease; CI, confidence interval; ET, estrogen therapy; EPT, estrogen and progestin therapy; RR, relative risk.

Risk of major CHD related to current hormone use and time of initiation of hormone therapy with respect to menopause.

Modified from Grodstein F, et al. *J Womens Health (Larchmt)*. 2006;15:35-44.

from the WHI study showed that the only significantly increased risk of CHD with hormone use occurred in women more than 20 years postmenopausal at enrollment and only in the first year of the trial.

A parallel WHI randomized trial evaluated the effect of 0.625 mg CEE without a progestin compared with placebo in 10,739 healthy postmenopausal women with a prior hysterectomy.¹⁶ This trial was stopped after a mean duration of 6.8 years. The HR for CHD in this study was 0.91 (nominal CI, 0.75-1.12). When the data from this study were analyzed by age group, the HR for CHD with estrogen use in women aged 50 to 59 years was 0.63 (CI, 0.36-1.08), for women aged 60 to 69 years, 0.94 (CI, 0.71-1.24), and for women aged 70 to 79 years, 1.11 (CI, 0.82-1.52).¹⁷ Thus, the data from this WHI trial indicate that use of estrogen by women aged

50 to 59 years reduces their risk of CHD by about 40%, similar to the observational studies in which the vast majority of the women started estrogen at this age.

Recent analyses: "Years since menopause" is key

The most recent publication of the WHI investigators characterized the effect of postmenopausal hormone therapy and risk of cardiovascular disease by both age and years since menopause at the time of enrollment.¹⁸ The results of this recent analysis of the data are similar to the prior analyses. The HR for CHD was 0.76 for all hormone therapy, compared with placebo for women less than 10 years since menopause at enrollment (TABLE 1). In this same short duration after menopause, CEE alone had an HR for CHD of

0.48, and for those receiving estrogen plus progestin it was 0.88. The HR for CHD in these 3 categories of analysis (no hormones, CEE alone, and CEE + MPA) for women who were 10 to 19 years postmenopausal was 1.10, 0.96, and 1.23, respectively. For women 20 or more years postmenopausal, it was 1.28, 1.12, and 1.66, respectively. In the latter group, only the HR for CEE alone and CEE + MPA were significantly increased.

Grodstein et al analyzed data from the Nurses' Health Study regarding time since menopause at initiation of therapy.¹⁹ These investigators determined that for women initiating hormone therapy within 4 years of menopause, there was a significantly reduced risk of CHD for estrogen alone (RR, 0.66) and for estrogen plus progestin (RR, 0.72) (TABLE 2). For women initiating therapy more than 10 years after menopause, the RR of CHD was 0.87 for estrogen alone and 0.90 for estrogen plus progestin. Neither of these figures was significantly different from the risk of CHD in women not taking estrogen.

In the nonhuman primate model, Mikkola and Clarkson showed that administration of estrogen immediately after oophorectomy reduced coronary atherosclerosis by 70% compared with placebo, but if estrogen treatment was delayed for 2 years—the equivalent of 6 human years—there was no reduction in atherosclerosis development (FIGURE 1).²⁰

Clinical decisions and the unified hypothesis

This large amount of data from randomized trials, observational studies, and findings in the animal model supports the belief that when estrogen is administered to women shortly after menopause, it retards the development of atherosclerosis by its beneficial effects on blood lipids and endothelial function. However, when large doses of oral estrogen are given to women older than 70 years, coronary artery occlusion can occur rapidly in some of these women with subclinical atherosclerosis by procoagulant and inflammatory mechanisms. These

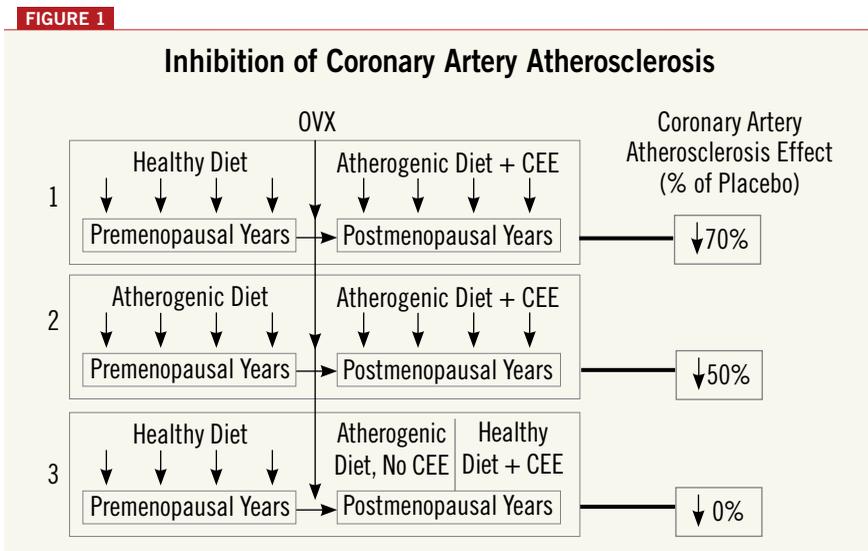
actions can cause rupture of coronary artery plaques and thrombosis in these narrowed vessels.

In 2005, two WHI investigators published a paper about postmenopausal hormone therapy: "Critical Reappraisal and a Unified Hypothesis."⁹ This thoughtful analysis of the WHI data is consistent with biological mechanisms, animal studies, human observational studies, and human clinical trials. The unified hypothesis predicts that hormone therapy begun at the time of menopause should result in a decrease of CHD over time. However, if hormone therapy is begun several years after menopause, there will be an increase in CHD events soon after starting therapy among women with subclinical coronary artery atherosclerosis, while the remaining healthy women will subsequently have a reduction in CHD events by retarding atherosclerosis development.

The authors of that paper stated that clinicians can use this unified hypothesis as a rational means to make clinical decisions. They explain that if clinicians administer estrogen to healthy postmenopausal women soon after menopause, estrogen will most likely delay the progression of atherosclerosis. Their analysis suggests that clinicians should avoid initiating high doses of oral estrogen in women older than 60 years because some of them may have subclinical coronary atherosclerosis and the prothrombotic and inflammatory effects of oral estrogen can cause coronary artery occlusion.

Unanswered questions

It remains to be determined whether transdermal estrogen, which has less of a procoagulant effect, has the same adverse action on women with subclinical atherosclerosis



CEE, conjugated equine estrogen; O VX, ovariectomy.

The relation of pre- and postmenopausal conditions to the degree of, or lack of, inhibition of coronary artery atherosclerosis.

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as oral estrogen does. In contrast to oral estrogen, which causes a 3- to 4-fold increased risk of venous thromboembolism (VTE), transdermal estrogen does not appear to increase the risk of VTE.²¹

The effect of the addition of progestin to estrogen on CHD events also remains to be determined.

Dr Mishell disclosed that he is a consultant to Barr Pharmaceuticals and Bayer Pharmaceuticals; and he is on the speakers' bureau of Bayer Pharmaceuticals.

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